Mishaps in drug regulatory processes: Insights into drugs approved by DCGI for COVID-19 treatment

A public viewpoint

8th National Bioethics Conference Program

Based on bits and pieces
compiled from here and there
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Regulatory provisions of current interest

- Accelerated approval process for clinical trials
- Restricted emergency use (REU) authorization for marketing and sale of drugs

Public & doctors have no clue what "restricted emergency use" means: if it means that there's

- suggestive evidence to grant drug for marketing and sale for given indication then large well-blind RCT (Phase III) cannot be waived.
- sufficient evidence on efficacy of the drug for given indication then why not full approval?

In USA, EUA is defined & approved products come with explicit conditions/facts to inform all stakeholders.
In India, pertinent results and protocol description need not be in public domain either.

- How do doctors prescribe such drugs?
- How do patients give informed consents?

REU approved drugs for COVID-19

- Remdesivir: severe COVID-19 (01.Jun.20); moderate to severe COVID-19 (19.Oct.20).
- Favipiravir: mild to moderate COVID-19 (19.Jun.20).
- Itolizumab: Cytokine reslease syndrome in mild to moderate ARDS due to COVID-19 (10.Jul.20, old formulation replaced with new formulation on 21.Sep.20).

Remdesivir:

- SOLIDARITY (WHO) and ACTT-1 (US): No reduction in mortality for severe cases. No significant clinical benefit.
- ACTT-1: Potential benefit in recovery time for section of moderate-to-severe cases. No significant reduction in mortality (high-flow oxygen or ventilation). (SOLIDARITY result differs; clinical benefit still under scrutiny)

Recommendations by SEC on Favipiravir proposals by Glenmark:

- 24.04.20: to conduct clinical trial (Phase III) with 150 patients (90 mild+ 60 moderate). Approval to be based on data from this trial & trials abroad.
- On 18.06.20:
  - REU granted while trial was ongoing;
  - to submit complete report on trial within 3 months;
  - to conduct active PMS on first 1000 patients to access the safety as well as efficacy.
- 22.07.20: Phase III results submitted for normal marketing approval but SEC opined to continue with REU and conduct PMS on 1000 patients at the earliest.

20.05.20: to conduct clinical trial (superiority study) for Umifenovir+Favipiravir vs Favipiravir in moderate patients. [09.10.20: NO superiority, 1 death in trial].

Efficacy & Safety of Favipiravir in Mild-to-Moderate COVID-19: **Open-Label** RCT, Phase 3

- Included asymptomatic cases, only 69.4% symptomatic patients.
- "Lack of statistical significance on the primary endpoint."
- Adverse events were observed in 36% of favipiravir and 8% of control patient.
- Paper itself defines mild disease as symptoms not requiring any or minimal therapeutic intervention.
- 10 authors: 1 local trial site PI, 9 (includes corresponding author) Glenmark Pharma employees; Glenmark funded; Published on 08.11.20.
- Claims protocol approved by IEC & DCGI (April 26, 2020), which seems contrary to SEC's recommendation on 24.04.20 (90 mild and 60 moderate).

Favipiravir NOT included in Clinical Management Protocol: COVID-19 by MOHFW, India.

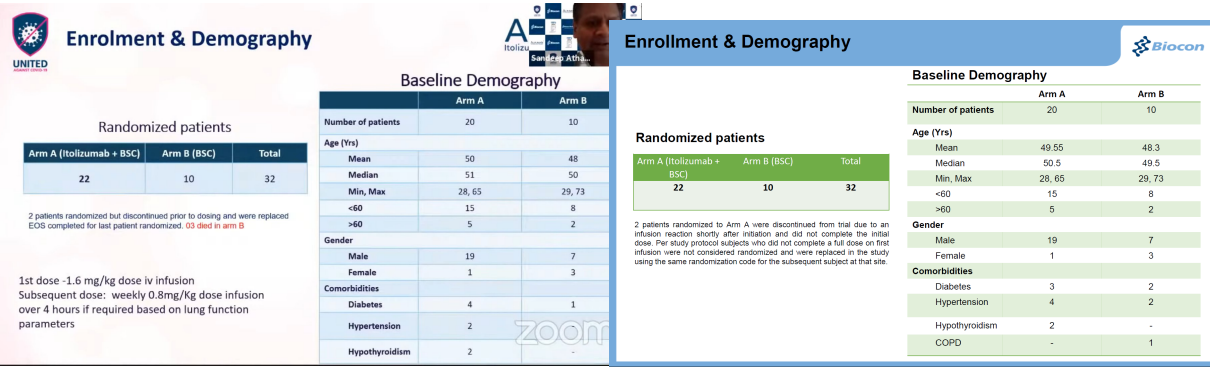
REU to Itolizumab: A baffling mystery

- Biocon presented Phase II (open-label RCT) proposal on 08.04.20. 1st enrollment on 01.05.20. CTRI has sample size 30 (20 treatment +10 control).
- On 28.05.20, SEC noted protocol violations during trial:
  1. Interim analysis was NOT part of the protocol.
  2. Randomization was NOT proper.
- On 18.06.20, protocol amendment accepted for ongoing Phase II trial (v3.0 to v5.0).
- REU granted on 10.07.20 after recommendation from SEC (the same day) with waiver of Phase III (trial for efficacy testing).
- 30.07.20: Phase IV on 300 patients. Safety to be only primary endpoint.

Itolizumab NOT included in Clinical Management Protocol: COVID-19 by MOHFW, India.

Itolizumab: Unsettling oversights & discrepancies in data diclosures

1 out of 2 patients replaced off Itolizumab arm died in 9 days.



Enrolment & Demography

Randomized patients

Arm A (Itolizumab + BSC)	Arm B (BSC)	Total
22	10	32

2 patients randomized but discontinued prior to dosing and were replaced
EOS completed for last patient randomized. 03 died in arm B

1st dose -1.6 mg/kg dose iv infusion
Subsequent dose: weekly 0.8mg/Kg dose infusion over 4 hours if required based on lung function parameters

Baseline Demography

	Arm A	Arm B
Number of patients	20	10
Age (Yrs)		
Mean	50	48
Median	51	50
Min, Max	28, 65	29, 73
<60	15	8
>60	5	2
Gender		
Male	19	7
Female	1	3
Comorbidities		
Diabetes	4	1
Hypertension	2	
Hypothyroidism	2	-

Enrollment & Demography

Biocon

Randomized patients

Arm A (Itolizumab + BSC)	Arm B (BSC)	Total
22	10	32

2 patients randomized to Arm A were discontinued from trial due to an infusion reaction shortly after initiation and did not complete the initial dose. Per study protocol subjects who did not complete a full dose on first infusion were not considered randomized and were replaced in the study using the same randomization code for the subsequent subject at that site.

Baseline Demography

	Arm A	Arm B
Number of patients	20	10
Age (Yrs)		
Mean	49.55	48.3
Median	50.5	49.5
Min, Max	28, 65	29, 73
<60	15	8
>60	5	2
Gender		
Male	19	7
Female	1	3
Comorbidities		
Diabetes	3	2
Hypertension	4	2
Hypothyroidism	2	-
COPD	-	1

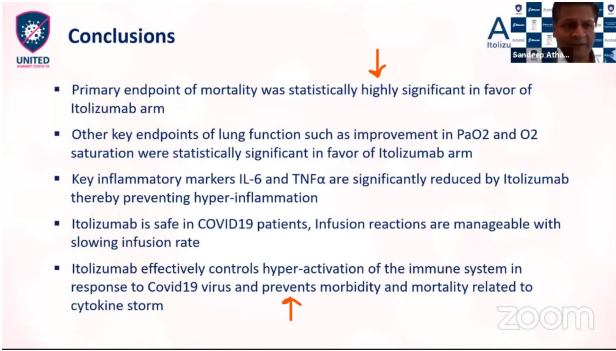
Only 1 female in Itolizumab arm. Unacceptable **gender disparity** in drug approval.

Itolizumab: Retrospective changes to trial design?

Pre-18.08.20, ONLY 1 primary endpoint. Post-18.08.20, CTRI has 6 primary endpoints.

Biological Division		
BIO/CT/20/00037 Itolizumab 25 mg/5 mL solution for intravenous infusion in vials	M/s Biocon Biologics India Limited	The firm presented the Phase II clinical trial results generated in COVID-19 patients. Details of Primary endpoint of mortality, other key endpoints of lung function such as improvement in PaO2 and O2 saturation were presented. Key inflammatory markers IL-6, TNFα etc were presented to have been reduced significantly with the drug

SEC for COVID-19, Dated 10.07.2020



26.11.20: Phase IV to include clinical outcome efficacy as PE along with safety. $\approx$ 2000 patients received Itolizumab under REU.

Itolizumab: Unsolvable riddles

- Was Itolizumab trial over by 07.07.20? A patient's video during press brief on July 13 implies NO.
- 21.09.20: Post approval (supplement) change permission to mfg for sale Itolizumab Inj (r-DNA origin) 100 mg/vial lyophilized powder. Listed under "new drug" for approved indications.
- Backed down from conducting global Phase III trial 2 weeks back.
- 01.12.20: pre-print on Phase II trial is released with lots of contradictory and dubious claims.
  1. 5 patients tested for safety (non-RCT) before RCT enrollment.
  2. Conducted per-protocol analysis; 4 primary endpoints.
  3. Claims to have DSMB & approvals from IECs/CDSCO; Biocon funded.
  4. 2 prominent authors from AIIMS Delhi, yet Itolizumab NOT mentioned in "FAQs on COVID-19 from AIIMS e-ICUs" (01.09.20).

"Off-label" investigator-led trials (contrary to clinical trial protocol)

TNN | Jul 13, 2020, 09:48 IST

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Dr Hemant Thacker

On Saturday, Indian authorities approved Biocon's drug itolizumab for treating moderate to severe Covid-19 patients. The story of how itolizumab—a medicine to treat skin rash psoriasisemerged as a 'repurposed' treatment for Covid-19 began in Mumbai. Dr Hemant Thacker was the first doctor in Mumbai to be called by Biocon executive chairperson Kiran Mazumdar-Shaw in early May to carry out a clinical trial. In an interview with TOI, he talks about the drug's "90% success" in the ICUs at Bhatia Hospital in Tardeo and Breach Candy Hospital.

Q: It is oft repeated that there are no specific treatments for Covid-19. What prompted you to undertake a clinical trial with itolizumab, a drug made in India?

A: Covid hit the scene real hard by about April 10 and I got into the thick of Covid patients by April second week. We didn't know much about the virus and had few drugs—azithromycin, doxycycline and tocilizumab, a monoclonal antibody supplied by a couple of companies. Tocilizumab was expensive at Rs 70,000, but we were